

Caries vaccine: A narrative review

Caries vaccine

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Abstract

Streptococcus mutans is the microorganism that is responsible for dental caries. A vaccine targeted at this microorganism could be beneficial to prevent dental caries. Even after various researches, successful immunization against dental caries remains an object yet to be achieved. The aim of the present narrative review to discuss various aspects of the dental caries vaccine.

Keywords

Dental caries; Vaccine; Immunization; Streptococcus Mutans

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Introduction

Dental caries is an irreversible disease of the calcified tissue of the teeth, which causes demineralization of the inorganic portion and destruction of the organic part of the teeth [1]. Dental caries is a multifunctional disease caused by environmental, host and agent factors. This disease not only impacts the individual but the whole family. People who cannot afford the treatment at the right time can face many complications at a later stage. This ultimately results in tooth loss, malfunctioning of the tooth, a problem in having a normal diet, which leads to many health-related issues.

Scientists research and figure out that prevention of dental caries can be done by creating a dental vaccine, which can simply be done by developing antibodies against dental caries. The dental vaccine is currently under development using the mechanism of inoculating against bacteria, particularly *S. mutans*, as its pathophysiology has various phases and each phase can be targeted for immunological intervention [2,3].

History suggested the success of vaccines is associated with disease eradication like chickenpox, which one way to achieve similar results for dental caries, which can effectively be applied in public health.

Many techniques, such as removing plaque mechanically by scaling, using pit and fissure sealants and using fluoride, were adopted and used for the prevention of dental caries. Most of these strategies are effective but these methods neither reduce the susceptibility of the host to get affected by dental caries, nor can reach a wide range of population. Therefore, in that scenario, the community needs an alternative approach that can help reduce the likelihood of dental caries [4]. An alternative to this approach to prevent the dental caries is the caries vaccine. The vaccine is well-suited and easy to implement in the public health system and can be available to more people, especially those who cannot afford or not able to visit the dentist on regular basis or cannot visit the dentist. This technique will surely help in taking prevention steps against dental caries in the community, especially in the younger age group.

Vaccine

Vaccines are immune biological substances designed to produce specific protection against a specific disease. It stimulates the production of protective antibodies and other immune mechanisms. Vaccines are prepared from living modified organisms, inactivated or killed organisms, extracted cellular fractions, toxoids, or a combination thereof.

Testing of Caries Vaccine

Smith (1993) tested on rats and concluded that a mucosal vaccine induces antibodies in saliva against *S. mutans*' surface structures, which provide adhesion to the tooth surface and reduce the bacterial acid production [5,6].

Immune response

Primary Response

Once an antigen is administered in the human or animal body, an induction period of 3 to 10 days must pass, during which antibodies are produced in the blood cell. Initially, IgM antibodies appear, which rise within 2-3 days and, reaching a peak, decline at the same speed. Secondly, IgG antibodies appear, the peak of which appears within 7-10 days, and it takes from a week to month to decrease. Due to the slow reduction, both B and T

lymphocytes produce memory cells, which are responsible for the immunological memory generated after immunization [7,8].

Secondary Response

Secondary or booster response is very different from the primary response. In this process, both IgM and IgG antibodies are produced. There is a short production of IgM antibodies and prolonged production of IgG antibodies in booster response. Vaccination and revaccination are the actual basis of the immune response and immunological memory [7,8].

Route of Immunization

To induce a protective immune response towards the antigens of the dental caries vaccine, various mucosal routes have been used, such as lymphoid tissues in the gut, nasal, brachial, or rectal sites. Various studies show that these mucosal routes used generated immune responses locally as well as remotely [9].

Oral

The oral route of administration has been used earlier, but studies show that it was not effective due to the determinant effects of the stomach acidity on the antigen. Masaaki et al., (1990) immunized mice orally with a recombinant *Streptococcus lactic* strain, which carries the structural gene for a surface protein antigen from *S. mutans* serotype C, resulted in significant salivary immunoglobulin A and serum immunoglobulin G responses [10]. In another study on monkeys by Michael et al., (2004), it was observed that secretory IgA induction was not significant [11]. Thomas (1992) suggested that the oral route is not ideal because stomach acidity affects antigens and the inductive site is also relatively far [12].

Intranasal

The intranasal route targeted the nasal associated lymphoid tissues. Many attempts are made to induce protective immunity at this site, which is anatomically closer to the oral cavity. Smith (2002) used the intranasal route on rats and observed a reduction in both *S. mutans* colonization and dental caries. [13]

Tonsillar

Many studies done on tonsillar-induced caries vaccine suggested that the ability to trigger immune responses in the oral cavity through tonsillar antigen application is a significant concern. A study on rabbit showed that repetitive tonsillar injection of a particular antigen can trigger the IgA producing cells in both minor and major salivary glands [12].

Minor Salivary gland

Minor salivary glands, because of their short and broad secretory ducts, are considered as a potential route for immunization, which is supported by the studies that show that labial application of GTF significantly reduces the *S. mutans* in saliva over a 6-week period [12].

Subcutaneous

Studies suggested that subcutaneous administration of *S. mutans* to monkey induce IgG, IgM and IgA antibodies, which can be found in the gingival crevicular fluid [14].

Rectal

This route can be used as an alternative in children with respiratory problems, which blocks the intranasal application of the vaccine.

Active Gingivo-Salivary route

Gingival crevicular fluid has been used as a route of

administration to localize the immune response, and both IgG and IgA levels have been found to increase in saliva [15].

Advances in dental vaccine

DNA Vaccine

A new anti-caries DNA vaccine significantly prevents dental caries. Studies have shown a successful reduction in dental caries and the cell surface protein PAc and the GTF domain (N-terminal catalytic sucrose-binding domain and C-terminal glucan-binding domain), which are known as virulence factors in *S. mutans* [2,13,14].

Delivery Systems and Adjuvants

Very few clinical studies demonstrated the efficacy of antigen-based active immunization against dental caries. Long-term IgA responses have rarely been achieved by topical application of a soluble peptide antigen to the oral mucosa. This has resulted in the redirection of research efforts to improve immunomodulators or adjuvants and delivery mechanisms that increase mucosal response to the vaccine against caries [2,13,16].

Synthetic peptides

The use of chemically synthesized peptides can strengthen the immune response and can prevent hypersensitivity reaction due to animal or human-derived antigens. Researches by using synthetic peptide have shown the immunogenicity of the alanine-rich Ag I/II region from *S. mutans*, while higher level of IgG antibodies were found in the protective immunity provided by mucosal immunization [2,13,16].

Coupling with Cholera and E. coli toxin subunits

The nontoxic unit of the Cholera Toxin (CT) has been shown to be a powerful mucosal immunoadjuvant, which can be used in combination with proteins to interrupt the proliferation of *S. mutans*. Mucosal immunity was improved when a small amount of CT or *E. coli* heat-labile enterotoxins (LT) was applied with peptides or soluble proteins [2,3,14].

Recombinant vaccines

The recombinant technology, used in the production of synthetic peptides, enables the expression of larger functional sequences. Avirulent *Salmonella* strains are one of the most effective vectors for the recombinant fusion technique. Effective oral immunization with recombinant *Salmonella* against *S. sobrinus* has been documented in rat studies [2,15,16].

Liposomes

Specifically, it has been used in anti-cancer research to target anomalous cells and facilitate successful drug delivery. Once it is used for the prevention of dental caries, a significantly improved mucosal immune response was observed by increasing the absorptions of M cells and the transmission of antigens to inductive tissue lymphoid elements [2,3,14].

Microcapsules and microparticles

Oral immunization with microspheres allows the vaccines to be released safely and in a controlled manner in the gut-associated lymphoid tissues (GALT) [2,14,16]. The local delivery system of Poly lactide-co-glycolide (PLGA) combines the advantage of a regulated and sustained release rate without triggering any inflammatory reaction.

Conjugate vaccines

A substantially enhanced immunogenic response to a T-cell-independent polysaccharide component can be achieved by

chemical conjugation of functionally related protein/peptide components with bacterial polysaccharides [2,14,16].

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These are solid particles combined with antigens along with biocompatible detergent and adjuvant carriers that can be helpful in dental caries prevention [2,13].

Plantigens and Plantibodies

Cariogenic microbes from plants perform better action against dental caries without causing side effects. CaroRX (2008), an improved plant-derived antibody and secretory IgA in nature, was developed in tobacco plants and seen to prevent dental caries [17].

Transgenic plants

The development of antibodies in transgenic plants like *Nicotiana tabacum* is one of the latest steps in the use of passive immunization. Rather than injection, these antibodies can be painted on the teeth [17,18].

Apples and Strawberries

David (2000) noted that injecting *S. mutans* blocking peptides into fruits like apples and strawberries minimizes dental caries [14,16].

Bovine milk and whey

Cattle immunization with *S. mutans* vaccine increases the polyclonal IgG antibodies in cattle milk and helps in the reduction of dental caries [2,14].

Egg-yolk

Hamada (1990) introduced hens' egg-yolk IgY antibodies, which can prevent the dental caries [2,13,14].

Recent Advances

The protein p1025 is the most recent significant development in the caries vaccine field. It replicates the surface structure of *S. mutans*. This has a major impact on *S. mutans* by causing false stimuli [19,20].

Future Prospects and Potential Impact

Since dental caries typically grows slowly and may occur during life, the immune defense can be expected to be equally long-lasting. Vaccine therapy is done to prevent infection. Since the association of *S. mutans* is seen as early as the 34th day in the mouth of the child, immunization against dental caries for people with more chances of infection must be started as early as the second year of life [4]. It is necessary to initiate subsequent immunization if the bacterial colonization is completed after the eruption of all primary teeth. The advantage of early immunization will continue until secondary teeth start to erupt. Two paths can be proposed for future studies. Primarily, to look for new target virulence genes or antigenic proteins to develop a vaccine, as well as using the best adjuvant and administration techniques that have been proven, and to further expand the use of nanotechnology. For example, a completely new protein (PstS), was examined by Ferreira et al., (2016), which showed significant results. Secondly, improving the best-proven animal studies vaccines up to the required standard [21]. Instead of working isolated, joint efforts should be made towards the most promising vaccine. In animal studies, outcome measures such as serum and salivary antibody measurements and their effectiveness in preventing both in-vivo and in-vitro *S. mutans* adherence should also be standardized. Furthermore, for different vaccines, the scores of caries should be calculated

and compared for effectiveness.

The objective of a vaccine against diseases is generally to provide a person with almost complete protection against infection and to achieve a sufficiently high prevalence of immunity in a population that breaks the transmission chain and cannot sustain the pathogen in the community. The biology of caries, however, is distinct from that of acute infections, and it is possible that immunization will not achieve maximum efficacy as with other modalities of action. However, the effectiveness of almost 50% may have significant effects on the burden of the disease and the related social and economic cost. It has been found that the majority of dental caries occurs in a high-risk population group, and targeting such an individual would increase its impact.

Conclusion

It is an understatement to note that more research is needed in the coming days to achieve an agent that can not only be used as a potent caries vaccine, but also be available at a lower cost to the general population. The issue of sufficient financial and infrastructural support is a major shortcoming of this research work, as the project is aimed at the elimination and eradication of dental caries, which are the bread and butter for the major portion of the dental health profession. However, dentists are looking forward to further research and development of caries vaccine that will be a blessing in the care of a patient with medical or physical difficulties, as well as in geriatric and pediatric dentistry.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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